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(54) Title: GENE EXPRESSION PROFILING OF INFLAMMATORY BOWEL DISEASE

(57) Abstract: The present invention relates to methods for identifying and/or classifying patients with inflammatory bowel diseases (IBD), particularly patients with Crohn's disease or ulcerative colitis. Gene expression profiling shows broad and fundamental differences in the pathogenic mechanism of UC and CD. The subject method is based on the findings that certain genes are differentially expressed in intestinal tissue of IBD patients compared with related normal cells, such as normal colon cells. That change can be used to identify or classify IBD cells by the upregulation and/or downregulation of expression of particular genes, alterations in protein levels or modification, or changes at the genomic level (such as mutation, methylation, etc), e.g., an event which is implicated in the pathology of inflammatory bowel diseases.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/41457

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, CHEM ABS Data, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>ZUO LI ET AL: "mRNA differential display of colonic mucosa cells in ulcerative colitis." JOURNAL OF SURGICAL RESEARCH, vol. 69, no. 1, 1997, pages 119-127, XP000877187 ISSN: 0022-4804 the whole document</p> <p style="text-align: center;">--- -/-</p> | 1-7 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

29 August 2002

Date of mailing of the international search report

17. 09. 2002

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INTERNATIONAL SEARCH REPORT

International Application No
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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | WILD G E ET AL: "ANALYSIS OF GENE EXPRESSION IN INFLAMMATORY BOWEL DISEASE BY DIFFERENTIAL DISPLAY PCR OF COLONOCYTE MRNA" GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, vol. 112, no. 4, SUPPL, 1997, page A1118 XP000877180 ISSN: 0016-5085 | 1-4 |
| Y | the whole document | 5-7 |
| X | DIECKGRAEFE B ET AL: "Characterization of mucosal gene expression in inflammatory bowel disease by direct hybridization to massively parallel oligonucleotide arrays" DIGESTIVE DISEASES AND SCIENCES, PLENUM PUBLISHING CO, US, vol. 114, no. 4, PART 2, 1998, page ABSTG3954 XP000877256 ISSN: 0163-2116 | 1-4 |
| Y | the whole document | 5-7 |
| X | DIECKGRAEFE B K ET AL: "Expression of the regenerating gene family in inflammatory bowel disease: potential role as an injury-induced tissue mitogen" GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, vol. 116, no. 4, PART 2, April 1999 (1999-04), page A601 XP000876959 ISSN: 0016-5085 | 1-4 |
| Y | the whole document | 5-7 |
| Y | FUNAKOSHI K ET AL: "Spectrum of cytokine gene expression in intestinal mucosal lesions of Crohn's disease and ulcerative colitis." DIGESTION, vol. 59, no. 1, January 1998 (1998-01), pages 73-78, XP001064174 ISSN: 0012-2823 | 1-7 |
| Y | the whole document | |
| Y | MAZZUCHELLI LUCA ET AL: "Differential in situ expression of the genes encoding the chemokines MCP-1 and RANTES in human inflammatory bowel disease." JOURNAL OF PATHOLOGY, vol. 178, no. 2, 1996, pages 201-206, XP001064186 ISSN: 0022-3417 | 1-7 |
| | the whole document | |

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International Application No
PCT/US 00/41457

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/41457

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | SATSANGI J ET AL: "GENETIC MARKERS IN INFLAMMATORY BOWEL DISEASE" CURRENT OPINION IN GASTROENTEROLOGY, GOWER ACADEMIC JOURNALS, LONDON, GB, vol. 12, no. 4, 1 July 1996 (1996-07-01), pages 322-326, XP000619908 ISSN: 0267-1379 the whole document | |
| P,X | WO 00 14283 A (DIECKGRAEFE BRIAN K ;UNIV WASHINGTON (US)) 16 March 2000 (2000-03-16) | 1-4 |
| P,Y | the whole document | 5-7 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/41457

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 12 relates to subject matter which the ISA is not required to search (Art.17 (2)(a)(i), R.39.1 (iii)).
2. ☒ Claims Nos.: 13, 17, 18
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 13,17,18

Present claims 5-7 relate to methods comprising the detection of the differential expression of an extremely large number of possible sets of genes comprising Interleukin-8. In fact, the claims contain so many possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been limited to methods comprising the detection of the differential expression of Interleukin-8 as such.

Claim 18 lack clarity (Art. 6 PCT), since it relates to a pharmaceutical preparation defined by reference to a desirable characteristic or property, namely modulating IBD gene expression. An attempt is made to define the pharmaceutical preparation by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Claims 13 and 17 are directed to a method of treatment of the human/animal body. Normally the search would have been carried out and based on the alleged effects of the compounds. However, because of what is mentioned above, no search could be performed.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/41457

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO 0014283 A | 16-03-2000 | US 6228585 B1 | 08-05-2001 |
| | | AU 5801799 A | 27-03-2000 |
| | | WO 0014283 A2 | 16-03-2000 |
| | | US 2002031767 A1 | 14-03-2002 |